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**Avian influenza and the pandemic  
threat:  
Global situation assessment**

Committee on International Relations,  
House of Representatives

Hearing on *Avian Flu: Addressing the Global  
Threat*

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## **Introduction**

The World Health Organization would like to thank Chairman Hyde and the Committee for the invitation to provide a statement in the context of its timely hearing on “Avian Flu: Addressing the Global Threat.” Just one month ago, on 7-9 November 2005, WHO co-hosted, with FAO, OIE, and the World Bank, a meeting in Geneva on avian and pandemic influenza. The meeting, which was attended by more than 600 experts from over 100 countries, marked the largest gathering held to date to assess the multiple threats arising from outbreaks of highly pathogenic avian influenza, caused by the H5N1 virus, that have been ongoing in parts of the world since mid-2003.

The meeting was considered unique in the number of participants, the high level of government representation, and the co-sponsorship of the four international agencies. For the first time, international and regional financial institutions were included to address economic issues and advise on mechanisms for funding priority interventions. The World Bank gave its estimate of the economic consequences of an influenza pandemic. Under the unique conditions of the 21st century, a pandemic could easily cost the world economy US\$ 800 billion within a year. Developing countries and aid agencies gave their assessment of how a pandemic would affect ongoing development projects: they would be ruined.

Discussions took place with a sense of urgency sharpened by the recent appearance of the virus in new countries, projections that further spread is almost certain, and an increase in reports of sporadic human cases. The meeting was followed a week later by confirmation of the first human cases of H5N1 infection in China.

Apart from taking stock of the current situation and related threats to human and animal health, the meeting aimed to make an inventory of precise needs, establish priorities, and map out ways to meet them. Mechanisms for matching these needs with rapid, adequate, and flexible funding were also explored. Discussions benefited from first-hand accounts from a diversity of countries either directly affected by outbreaks in birds and humans or considered at high risk. Expressions of need were open and candid. Several front-line countries frankly admitted their inability to deal with a disease of this nature on their own, despite full awareness of what failure would mean for the international community. These presentations helped give the shared sense of urgency a focus by defining specific needs and challenges. They also moved the discussion forward by suggesting concrete lines of action.

Deep concern about the consequences of a pandemic steered discussion, on human health matters, towards consideration of two main sets of actions. These were aimed at (1) preventing the emergence of a pandemic virus or, should this prove impossible, delaying the initial international spread of a pandemic, and (2) preparing all countries to cope with a pandemic in ways that mitigate morbidity and mortality and also reduce economic and social disruption. Participants agreed that the threat of a pandemic was of shared and significant concern for all countries, and that actions to prevent a pandemic or mitigate its consequences were likewise a shared responsibility of countries.

Given the high level of concern and sense of solidarity, it is understandable that participants readily agreed on ten main conclusions and a 12-point set of actions. These are reproduced in Annex 1. Following the meeting, WHO prepared a five-pronged strategic action plan, which sets out strategies for acting pre-emptively now and, should these actions fail, for mitigating the consequences of a pandemic. This plan is summarized in Annex 2. As stated by the WHO Director-General at the close of the meeting, implementation of the recommended actions will begin immediately. A follow-up meeting, to decide on funding priorities and mechanisms, will be held in Beijing in early January 2006.

As requested, this statement provides a global overview of the epidemiological situation, stressing features that fuel concerns that a pandemic may be imminent. A summary of the situation in South-East Asia, Russia, and Europe is provided, together with an explanation of the roles and responsibilities of WHO in responding to the crisis. The status of pandemic vaccines and antiviral drugs – the two medical interventions for reducing morbidity and mortality during a pandemic – is assessed in terms of prospects for their availability, soon enough and in sufficient quantities. As guidance for the international response, some relevant lessons from the SARS experience are briefly described.

## **Reasons for concern about the H5N1 influenza virus**

- *The virus causes extremely severe disease in humans.*
- *It has considerable pandemic potential.*
- *The source of human exposure is not easily removed.*
- *The virus is evolving in ominous ways.*
- *The world may be on the brink of another pandemic.*

**Severe human disease.** Of all influenza viruses that circulate in birds, the highly pathogenic H5N1 virus, currently becoming widespread in animals, is of greatest concern for human health for several reasons. First, though avian influenza viruses rarely cross the species barrier to infect humans, H5N1 has done so on three occasions since 1997. This virus has also caused by far the greatest number of human cases of very severe disease and the greatest number of deaths. Unlike normal seasonal influenza, where infection causes only mild respiratory symptoms in most people, the disease caused by H5N1 follows an unusually aggressive clinical course, with rapid deterioration and high fatality. Primary viral pneumonia (which does not respond to antibiotics) and multi-organ failure are common. For unknown reasons, most cases have occurred in previously healthy children and young adults.

**Pandemic potential.** The H5N1 virus has considerable potential to spark another influenza pandemic. At present, all conditions for the start of a pandemic have been met save one: the establishment of efficient and sustained human-to-human transmission. Each additional human case gives the virus an opportunity to combine with other viruses or adapt in ways that allow it to spread easily among humans. The risk of human cases persists as long as the virus continues to circulate in birds; the virus will not be eliminated from birds for some years to come.

**A tenacious virus in poultry.** The current outbreaks in poultry are historically unprecedented in their scale and geographical scope. Never before have so many birds been affected in such a large number of countries. Despite intense control efforts, the virus has become firmly entrenched in large parts of Asia. On numerous occasions, countries thought close to control have experienced setbacks as outbreaks recurred and then spread rapidly. Timeframes for controlling the disease are now being measured in years. Recent evidence that wild waterfowl are now carrying the virus in its highly pathogenic form is particularly worrisome, as all experts agree that elimination of the virus from wild birds is impossible.

**An ominous evolution.** Like all influenza viruses, H5N1 is notoriously unstable and unpredictable. In an historically unprecedented situation involving a constantly changing virus, unusual developments can be expected, and these have occurred. During the past 18 months, the virus has evolved in ways that increase the complexity of control and heighten concern about the pandemic threat.

Domestic ducks can now excrete lethal virus without showing signs of illness, thus acting as a “silent” reservoir of the virus, perpetuating transmission to other birds. This adds yet another layer of complexity to control efforts and removes the warning signal for humans to avoid risky contact with sick or affected animals. Second, the relationship between the virus and its natural

animal reservoir, wild waterfowl, appears to have changed, possibly for the first time in centuries. The spring 2005 die-off of more than 6,000 migratory birds at a nature reserve in central China, caused by highly pathogenic H5N1 virus, was highly unusual and probably unprecedented. Scientists are increasingly certain that at least some wild waterfowl are now harbouring and excreting highly pathogenic H5N1 virus and carrying this virus with them along their migratory flyways. The recent spread of the virus to Russia and parts of Europe is thought to have occurred via this wild-bird vector; spread to additional areas is considered inevitable.

When compared with H5N1 viruses from 1997 and early 2004, viruses now circulating are more lethal to experimentally infected mammals and survive longer in the environment. Mammalian species previously considered resistant to infection have developed disease and can spread it to others within their species. Expansion of the mammalian host range of the virus is of concern as it gives this purely avian virus more opportunities to adapt to a form that spreads more easily among mammals, including humans.

Perhaps most significantly, recent research on both human and animal viruses circulating in Asia in 2005 has detected several mutations, some of which may affect transmissibility in humans. Research following recent reconstruction of the highly lethal 1918 pandemic virus determined that this virus was entirely avian and may have evolved along an evolutionary pathway similar to that being seen with the H5N1 virus.

**On the brink of a pandemic.** For all these reasons, WHO and international experts believe that the world is now closer to another influenza pandemic than at any time since 1968, when the last of the previous century's three pandemics began.

A pandemic is caused by a new influenza virus that has either never circulated in humans or has not done so for a number of years. Because humans will have little if any immunity to this "foreign" virus, susceptibility is virtually universal. This lack of immunity also results in more severe disease than seen during seasonal epidemics of normal influenza. The result is a worldwide epidemic (pandemic) that sweeps through susceptible populations, rapidly encircles the globe, and causes excess morbidity and mortality, usually far above that seen during seasonal epidemics. Whereas seasonal influenza usually has its most severe effects on a limited number of risk groups (the very young and the elderly, persons with underlying chronic disease or compromised immune systems), pandemics can cause severe illness and deaths in all age groups, including the young and healthy. The newness of the virus also means that existing vaccines will not confer protection.

With the H5N1 virus now considered endemic in large areas, and spreading to new ones, the probability that a human pandemic will occur has increased. As no virus of the H5 subtype has ever circulated widely in human populations, human vulnerability to infection with this virus will be universal. On the positive side, experts anticipate that the virus will lose some of its virulence (the present case fatality rate is higher than 50%) when it improves its transmissibility; this is not, however, known with certainty. Historically, pandemics have encircled the globe in 6 to 9 months, even at times when international travel was mainly by ship. Today, experts believe that the first pandemic of the 21st century will reach all parts of the world within 3 months.

## **Status of H5N1 outbreaks in South-east Asia**

The recent history of avian influenza in Asia begins in 1996, when a highly pathogenic H5N1 virus was isolated from a farmed goose in Guangdong Province, China. The following year, Hong Kong experienced poultry outbreaks, caused by this virus, on farms and in wet markets. Coincident with these outbreaks, the first instances of human infections with the H5N1 virus were recorded in Hong Kong. Altogether, 18 cases, of which 6 were fatal, were identified in

that outbreak. This event changed scientific thinking about how pandemic viruses might emerge, raising – for the first time – the possibility that an entirely avian virus, capable of causing severe human disease, could be the origin of the next pandemic if given enough opportunities to infect humans and adapt to them. The destruction of Hong Kong's entire poultry population of around 1.5 million birds within 3 days is thought by some experts to have averted an influenza pandemic at that time. Human cases were again detected in Hong Kong in February 2003 in members of a family with a recent travel history to Fujian Province, China.

After a period of quiescence, the virus resurfaced at some time during mid-2003, and quickly erupted into the largest outbreaks of this disease seen in history. Beginning in late December 2003, outbreaks of highly pathogenic H5N1 avian influenza in poultry were reported in nine South-east Asian nations (listed in order of reporting): Republic of Korea, Vietnam, Japan, Thailand, Cambodia, Lao People's Democratic Republic, Indonesia, China, and Malaysia. Of these countries, three have controlled their outbreaks and are now considered disease-free: Japan, Republic of Korea, and Malaysia. Elsewhere, experience shows how firmly entrenched this virus has become and how difficult its complete elimination will be. Despite the death or destruction of around 160 million birds, at a cost to agriculture of an estimated US\$ 10 billion, the virus is now considered endemic in Indonesia and Viet Nam and in some parts of Cambodia, China, Thailand, and possibly also Lao PDR.

In late December 2003, human infections were identified in people exposed to infected poultry in Vietnam. Since then, just under 140 human cases have been laboratory confirmed in five Asian countries (Cambodia, China, Indonesia, Thailand, and Viet Nam), and more than half of these people have died. At present, however, the species barrier is significant. The number of human cases is small in comparison with the huge number of birds affected, over large geographical areas, for two years, and under circumstances offering abundant opportunities for human exposure to occur.

Control of the disease in animals faces several serious challenges, and opportunities for further human infections to occur will persist. In some affected countries, up to 80% of poultry production takes place in small backyard flocks, where surveillance is weak, reporting is poor, and control measures are difficult to implement. These are the areas of greatest concern for human health: to date, the majority of human cases have been linked to exposure to infected household poultry in rural and periurban areas. In these areas, poultry usually roam freely scavenging for food, often entering homes or sharing outdoor areas where children play. Populations traditionally sell or consume birds when signs of illness appear in a flock. This practice has proved hard to change, especially when poultry are a principal source of income and food and cannot be wasted. Behaviours thought to carry a high risk of infection include the home slaughtering, butchering, defeathering, and preparation for consumption of diseased birds.

Most affected countries cannot adequately compensate farmers for culled poultry, thus discouraging the reporting of outbreaks in the rural areas where the vast majority of human cases have occurred. Veterinary services frequently fail to reach these areas. Detection of human cases is impeded by patchy surveillance. Moreover, the initial symptoms of H5N1 infection mimic those of many other diseases commonly seen in affected countries, further increasing the risk that cases are being missed. Diagnosis of human cases is impeded by weak laboratory support and the complexity and high costs of testing. Few affected countries have the staff and resources needed to thoroughly investigate human cases and, most importantly, to detect and investigate clusters of cases – an essential warning signal that the virus may be improving its transmissibility among humans. Because of this inadequacy of the surveillance system, the possibility that human cases are occurring – undetected and unreported – cannot be ruled out. Such lapses are of critical importance to the international community, as timely case reporting constitutes the backbone of the early warning system for detecting the emergence of a pandemic virus. Unless the situation improves, early warning signals that the virus has increased its transmissibility among humans will be missed, and the world will once again be taken by surprise when international spread of a pandemic begins, at which time opportunities

for pre-emptive action will be lost. Once a fully transmissible virus emerges, pandemics are considered unstoppable.

## **The role of WHO in field-level operations**

WHO staff at country offices work closely with ministries of health, assist in the diagnostic confirmation and field investigation of cases, and provide the interface between these ministries and the international community. Diagnostic confirmation of human cases is technically challenging; work with the virus can be safely performed only in laboratories with a high level of biosecurity, and such laboratories are rarely available in affected countries. For these reasons, WHO provides diagnostic support through its coordination of the global network of influenza laboratories specialized in work on the H5 virus subtype. In the US, this network includes the US Centers for Disease Control and Prevention (CDC) of the Department of Health and Human Services and a second laboratory, for animal influenza viruses, at St Jude Children's Research Hospital in Memphis. The US Naval Medical Research Unit 2 (NAMRU 2), located in Jakarta, Indonesia, has been another source of rapid diagnostic support, particularly for cases in Indonesia that have been occurring since mid-September 2005. All of these laboratories are equipped to handle H5N1 viruses at the highest level of biosecurity. WHO country staff arrange for patient samples to be shipped safely to these laboratories for diagnostic confirmation. These laboratories also conduct molecular studies of viruses to look for genetic changes that might signal improved transmissibility and to ensure that work on a pandemic vaccine (which must closely match circulating virus strains) remains on track.

While molecular studies of the virus are one important part of the early warning system, rapid detection and investigation of human cases are even more important, particularly when clusters of cases, closely related in time and place, are detected. Investigations of possible human-to-human transmission are complex. In many areas, the virus is now so pervasive that it is difficult to determine, when clusters occur, whether people acquired the virus from some shared environmental source or each other. At the request of governments, WHO regularly sends international teams of experts, drawn from institutions in its Global Outbreak Alert and Response Network (GOARN), to conduct on-site investigations when unusual disease events of potential international public health importance – such as H5N1 cases in humans – occur. Such teams also assist in the development of national surveillance and diagnostic capacity. Experts from the CDC are usually part of these teams. WHO also procures essential supplies to support laboratory work and the clinical management of cases. Video conferences and teleconferences are regularly held with international experts to gather consensus on the evolution of the threat and to assist WHO in its overall assessments of the situation.

## **The outbreaks in Russia and Europe**

Beginning in late July 2005, highly pathogenic H5N1 was detected in wild and domestic birds in Siberia (Russia) and in adjacent parts of Kazakhstan. Almost simultaneously, Mongolia reported H5N1 in a large number of dead migratory birds. In Russia, poultry outbreaks have since spread westward towards Europe. In October 2005, Turkey and Romania confirmed H5N1 outbreaks in poultry, and Croatia detected the virus in dead migratory birds. In December 2005, Ukraine detected outbreaks in domestic birds. All newly affected areas are located along the flight paths of migratory birds. Deaths of wild and domestic birds in several other areas, including parts of Africa that lie on migratory routes, are under investigation.

Throughout Europe, vigilance for the appearance of outbreaks in wild and domestic birds and for the occurrence of associated human cases is high. Outbreaks in animals have been detected and reported quickly, and extensive control measures have followed immediately. WHO epidemiologists and virologists have assisted in investigations, when requested. Diagnostic

reagents have been sent to national laboratories, and WHO has provided training in H5N1 diagnostic techniques. Viruses have been shared internationally and are undergoing analysis at WHO reference laboratories. These laboratories have also helped to rule out, authoritatively, the many false rumours of human cases. To date, no human cases have been associated with any of these newer animal outbreaks outside Asia.

Several high-level meetings of European ministries of health and agriculture have been held to discuss the avian influenza threat and consider the best preventive and control measures. These meetings have led to the development or refinement, with WHO assistance, of pandemic response plans in the vast majority of European countries.

Europe has areas with dense poultry populations and has experienced outbreaks of highly pathogenic avian influenza in recent years, though caused by influenza viruses other than H5N1. While the further evolution of poultry outbreaks caused by H5N1 in Europe cannot be predicted, prompt detection of outbreaks and the rapid introduction of control measures will hopefully prevent the virus from establishing endemicity outside its present epicentre in South-east Asia. Differences in farming systems between western Europe and Asia, and the greater availability of resources in Europe, should give established control measures a greater chance of success. Many European countries do, however, have rural areas where poultry flocks are kept in close contact with households, and these areas could pose a heightened risk of human cases should outbreaks in poultry become established. Of particular concern are continuing reports of fresh outbreaks in Romania. As the H5N1 virus can persist in the environment for long periods at cold temperatures, authorities in Russia are concerned that fresh outbreaks could occur spontaneously in the spring. Moreover, bird migrations are recurring events; the risk of fresh outbreaks associated with this vector will persist.

## **Vaccines and antiviral drugs**

Vaccines and antiviral drugs are the most important medical interventions for reducing morbidity and mortality during a pandemic. Vaccines are the most important intervention for conferring population-wide protection, but vaccine effectiveness requires a close match with the actual pandemic strain of the virus. Because a pandemic strain, capable of efficient and sustained human-to-human transmission, does not yet exist, the specific pandemic vaccine does not yet exist either. As no country will have adequate vaccines at the start of a pandemic, antiviral drugs assume particular importance as the only possible medical intervention for protecting priority groups pending the arrival of vaccines. Antiviral drugs might also be used to contain or delay the spread of a pandemic at its source. For both vaccines and antiviral drugs, present constraints – which are considerable – mean that most developing countries will have no or very limited access to either throughout the course of a pandemic.

**Vaccines.** Vaccines are considered the first line of defence during a pandemic. For several reasons, no country will have adequate supplies of vaccine at the start of a pandemic and for many months thereafter. Large-scale commercial vaccine production of a pandemic vaccine is not expected to commence until about three to six months following the emergence and characterization of a pandemic virus.

Manufacturing capacity for influenza vaccines is overwhelmingly concentrated in Europe and North America. Current maximum production capacity – estimated at around 420 million doses of trivalent seasonal vaccine per year – falls far below the demand that will arise during a pandemic.

WHO, through its network of specialized influenza laboratories, has constantly monitored the evolution of seasonal viruses and also of the H5N1 virus since its initial infection of humans in 1997. These laboratories prepare the prototype virus strain that is being provided to industry as the “seed” for vaccine development. Constant molecular analyses of viruses, conducted by

these laboratories, help ensure that this “seed” strain continues to closely match the genetic characteristics of currently circulating viruses. This activity is particularly important in view of mutations in the H5N1 virus detected during 2005.

During the November 2005 meeting on pandemic influenza, the availability of pandemic vaccines, shortly after the start of a pandemic and in sufficient quantities, was identified as the greatest challenge facing the international community. If this challenge is not met, access to vaccines will almost certainly be confined to populations in countries having domestic vaccine manufacturing capacity. At present, around 80% of vaccine manufacturing capacity is concentrated in Europe and North America. Just under 20 countries have domestic manufacturers producing influenza vaccines for the seasonal influenza viruses; several of the largest of these companies are presently working on the development of a pandemic vaccine. Some of these development projects have reached the stage of clinical trials; clinical trials of other candidate vaccines are expected to begin shortly. In early November 2005, WHO convened a meeting of influenza vaccine manufacturers to assess progress in the development of a pandemic vaccine and to conduct an inventory of global manufacturing capacity, particularly in developing countries. While overall capacity looks somewhat more encouraging than one year ago, if a pandemic were to begin within the next few months, no company would be ready to move immediately into commercial production of a pandemic vaccine. Several companies have plans to expand production capacity, but these plans will not be realized for at least another 2 to 3 years.

Finite capacity to produce antigen – the component of the vaccine that elicits the immune response – is a critical limiting factor. Strategies for producing vaccines that are effective, yet use less antigen, could profoundly increase current manufacturing capacity. At present, little knowledge exists to guide formulation of an influenza vaccine that is both effective and economizes on the use of antigen. Clinical trials are under way to test different formulations, and these trials will provide some answers. WHO has encouraged companies to test vaccine formulations that include an adjuvant. This substance boosts the immune response, and theoretically could allow adequate protection at lower quantities of antigen. Work on this approach is also under way.

As a pandemic vaccine needs to be a close match to the actual pandemic virus, commercial production cannot begin prior to emergence and characterization of the pandemic virus. WHO has, however, encouraged industry and regulatory authorities to develop fast-track procedures for licensing and marketing authorization of a pandemic vaccine, and this has been done.

WHO is using international meetings to urge the international community to find ways to increase manufacturing capacity and ensure that developing countries have access to an effective vaccine at an affordable price. As another strategy, WHO has provided direct assistance to some developing countries engaged in work on a pandemic vaccine. On current trends, however, most developing countries will have no access to a vaccine during the first wave of a pandemic and perhaps throughout its duration.

**Antiviral drugs.** Pending the availability of vaccines, several antiviral drugs are expected to be useful for prophylaxis (prevention of illness) or treatment purposes. Two drugs (in the neuraminidase inhibitors class), oseltamivir (commercially known as Tamiflu) and zanamivir (commercially known as Relenza), have been shown, in laboratory studies, to reduce the severity and duration of illness caused by seasonal influenza. The efficacy of the neuraminidase inhibitors depends on their administration within 48 hours after symptom onset. For cases of human infection with H5N1, the drugs may reduce the severity of disease and improve prospects of survival, if administered early, but clinical data are limited. The H5N1 virus is expected to be susceptible to the neuraminidase inhibitors.

Another class of antiviral drugs, the M2 inhibitors amantadine and rimantadine, could potentially be used against pandemic influenza, but resistance to these drugs may develop



rapidly and this could significantly limit their effectiveness. Some currently circulating avian H5N1 strains are fully resistant to the M2 inhibitors, while others remain fully susceptible.

For the neuraminidase inhibitors, the main constraints – which are substantial – involve limited production capacity and a price that is prohibitively high for many countries. Because of the complex and time-consuming manufacturing process, the sole manufacturer of oseltamivir is unable fully to meet demand and faces a backlog of orders. At present manufacturing capacity, which has recently quadrupled, it will take a decade to produce enough oseltamivir to treat 20% of the world's population. The complex manufacturing process also makes it difficult to transfer production technology to other facilities. Nonetheless, strategies for doing so are being explored as a matter of urgency, and particular attention is being given to the option of manufacturing oseltamivir in developing countries.

Since supplies are severely constrained, countries now stockpiling antiviral drugs need to decide in advance on priority groups for administration, particularly for prophylactic purposes. Frontline health care workers would be an obvious first choice, but such decisions are the responsibility of governments. While antiviral drugs can confer some measure of protection pending the availability of vaccines, these drugs should not be used to perform the same public health function as vaccines – even if supplies would permit. The mass administration, for prophylactic purposes, of antiviral drugs to large numbers of healthy people for extended periods is not recommended, as this could accelerate the development of drug resistance.

Following a donation by industry, WHO will have a dedicated stockpile of antiviral drugs (oseltamivir), sufficient for 3 million treatment courses, by early 2006. These drugs are strictly reserved for use in the first areas affected by an emerging pandemic virus. Recent studies, based on mathematical modelling, suggest that these drugs could be used prophylactically near the start of sustained human-to-human transmission to reduce the risk that a fully transmissible pandemic virus will emerge or at least to delay its international spread, thus gaining time to augment vaccine supplies. The drugs will be stored centrally; WHO has considerable experience in the rapid dispatch of medical supplies during emergencies.

The success of this strategy, which has never been tested, depends on several assumptions about the early behaviour of a pandemic virus, which cannot be known in advance. Success also depends on excellent surveillance and logistics capacity in the initially affected areas, combined with an ability to enforce movement restrictions in and out of the affected area. To increase the likelihood that early intervention using the WHO rapid-intervention stockpile of antiviral drugs will be successful, surveillance in affected countries needs to improve, particularly concerning the capacity to detect clusters of cases closely related in time and place.

Should the virus behave in ways that preclude rapid intervention to contain a pandemic or delay its spread, drugs in the stockpile will be used to provide treatment in the initially affected countries.

## **Urgent activities in an emergency situation**

The seriousness of the present threat to international public health calls for emergency actions calculated to provide the greatest level of protection as quickly as possible. The most reliable and predictable way immediately to improve the world's defences is to build on existing structures and mechanisms that have worked well in similar emergencies.

No health emergency on the scale of a severe influenza pandemic has confronted the international community for several decades. At the same time, however, WHO and its international partners have acquired considerable experience in responding to outbreaks of new and epidemic-prone diseases that have occurred, in unprecedented numbers, in recent years.

Each outbreak presents a unique set of problems that have to be solved, innovatively and quickly, under emergency conditions. Each outbreak response has left WHO and its partners with more experience and more technical innovations to draw on when crafting a response plan for the next unique event. These experiences, and the existing mechanisms that sustain them, can be immediately adapted to provide a strengthened response near the start of a pandemic. WHO now has a flexible fund of operational options to draw on, and these are backed by standardized protocols for outbreak investigation and standard operating procedures as well as by considerable experience under a variety of country settings.

The type of support that can be provided by WHO and its institutional partners in the Global Outbreak Alert and Response Network (GOARN) will probably be most decisive in the first countries experiencing evidence of efficient human-to-human transmission.

For almost two years, several Asian nations have undertaken resource-intensive activities in the interest of protecting the international community from an unpredictable, yet potentially catastrophic event. These activities have been undertaken despite low national budgets for health care and the presence of many other high-priority diseases. Many of these activities, specific to the control of avian influenza and prevention of another pandemic, must now be given full international support. Only through such support will the international community receive the data needed for a reliable risk assessment which, in turn, guides many interventions to be undertaken according to the various WHO phases of pandemic alert. If this support is not provided, triggers for scaling up activities will be missed and the world may, once again, be taken by surprise when a pandemic virus emerges.

## **Lessons from SARS**

The international outbreak of severe acute respiratory syndrome (SARS) was a watershed event. It revealed how much the world has changed in terms of the impact that outbreaks of a severe new disease can have in a highly mobile and closely interconnected world. During a fortunately brief stay in its new human host, the SARS virus travelled rapidly along the routes of international air travel to infect more than 8,000 people in about 30 countries. Of these people, SARS killed just under 800.

The SARS experience was remarkable in several ways. It caused enormous economic damage and social disruption in areas far beyond the outbreak sites. The previous estimates of the economic costs of that outbreak, US\$ 30 billion, are now considered conservative. The SARS experience showed that decisive national and international action, taking full advantage of modern communication tools, could prevent a new disease from establishing endemicity. It raised the profile of public health and appreciation of the importance of international cooperation in health to new heights.

SARS primed politicians to understand both the far-reaching consequences of outbreaks and the need to make rapid containment a high priority. SARS also stimulated efforts to find ways to make the impact of the next international outbreak less dramatic.

Many – but not all – of these lessons are useful as the world braces itself against the prospect of another human influenza pandemic. The unprecedented scientific and medical collaboration that characterized the SARS outbreak, with leading experts openly sharing their latest findings, can also be expected to help the world understand a new pandemic virus quickly and translate this new knowledge rapidly into practical advice for control. The threat posed by the H5N1 virus has already attracted political attention at the highest levels, including the launch of the US-initiated International Partnership for Avian and Pandemic Influenza. This is valuable to advance necessary prevention and preparedness activities worldwide at national, regional, and global levels.

Unlike SARS, however, pandemic influenza is considered unstoppable once international spread is fully under way. The classic public health interventions – screening, early detection of cases, and tracing and follow-up of contacts – that proved decisive in containing SARS will not be sufficient to interrupt the transmission of a pandemic influenza virus. Because influenza virus can be transmitted prior to the onset of symptoms, programmes to screen for symptoms will not detect all carriers. The very short incubation period leaves too little time to conduct contact tracing. Each influenza patient can be expected to transmit the virus to another person within 2 days; the number of cases will grow exponentially. Moreover, influenza spreads easily through the air via coughing or sneezing; SARS transmission required close face-to-face contact with a patient.

One important lesson from SARS is paramount: the importance of real-time monitoring of the evolving situation, supported by advice from the world's best experts, and immediate communication of information. The effectiveness of non-pharmaceutical measures for control will depend on the characteristics of the pandemic virus (attack rate, virulence, principal age groups affected, patterns of spread within and between countries), and these cannot be known in advance. After a pandemic is declared, WHO will monitor its evolution in real time and issue updated advice accordingly. Recommendations about the most effective control measures will therefore become more precise as the epidemiological potential of the virus unfolds. Virtual networks of experts will advise WHO on such issues as projected patterns of spread, modes of transmission, laboratory diagnosis, and clinical management of patients, and this information will be communicated immediately. All experts hope that use of good risk communications practices at every level and an informed public will facilitate the smooth implementation of control measures, while also reducing some of the social and economic disruption that make pandemics such dreaded events.

WHO will continue to work with its 192 Member States and other international organizations on an ongoing basis to assess the threat of pandemic influenza and to help improve preparedness and response to mitigate the consequences of a pandemic.

## **Annex 1: International recommendations for responding to the pandemic threat**

Over the last several years WHO has issued a number of documents to assist countries, at various levels of development, in preparing their strategies and detailed responses to pandemic influenza. These technical and strategic documents are available on the WHO Website ([www.who.int](http://www.who.int)). Last month, WHO launched a new website ([http://www.who.int/csr/disease/avian\\_influenza/pandemic/en/index.html](http://www.who.int/csr/disease/avian_influenza/pandemic/en/index.html)) devoted to assessment of the influenza pandemic threat.

During the 7-9 November 2005 international meeting on avian and pandemic influenza, participants agreed on ten main conclusions and twelve recommendations for integrated and immediate action.

### **Conclusions**

1. Minimizing the threat at source to both animal and human populations through rapid reduction of the viral burden of H5N1 is essential. This entails timely notification of outbreaks in birds, poultry culling and vaccination as indicated, including "backyard" flocks, and provision of appropriate compensation for farmers.
2. "Early warning" and surveillance systems for animal and human influenza are critical to effective response. The current window of opportunity to intervene is measured in days. Transparent and immediate reporting is essential.
3. The introduction of avian infection with H5N1 to other countries is predicted, following the patterns of migratory birds, and as a result of production systems and market practices. Other strains of avian flu are also an ongoing and emerging threat and must be monitored. Strengthened veterinary services are a crucial aspect of detection and response. Open sharing of virus samples is essential. Quality assured animal vaccines produced to international standards should be used in healthy poultry when appropriate.
4. At present many governments are not ready to cope with outbreaks, still less a pandemic. Preparedness is vital in every country, in every region. Integrated country plans will build on and strengthen existing systems and mechanisms. They will be comprehensive, costed, and evaluated. Response mechanisms should be rehearsed through simulation exercises. These plans will include protection of vulnerable groups such as children, refugees and displaced populations.
5. Resources needed to slow down or contain the emergence of a pandemic are insufficient. Supplies of antiviral drugs currently do not meet potential demand. Issues remain of equitable access to medicines and deployment of stockpiles.
6. A universal non-specific pandemic vaccine may be the ultimate protective solution for human influenza. "Smart" solutions are being investigated. Issues of technology transfer, resolution of licensing and regulatory obstacles, sustained use of good manufacturing practices and pre-qualification are under discussion. Predictable, increased orders for seasonal flu vaccine will support greater manufacturing capacity, including in developing countries.
7. Communications. The recent series of high-level meetings on avian influenza and human pandemic influenza have successfully created a shared agenda. The public needs clear, regular, reliable information. Civil society, nongovernmental organizations and other community groups must be involved.
8. A rich array of resources is potentially available to support government and institutional efforts. Countries that have successfully controlled outbreaks of avian influenza are prepared to help others.

9. Mechanisms for donor support are in place. There is broad commitment to minimize transaction costs of international support through alignment and harmonization. International support to country plans should supplement national resources, as well as existing donor resources, and should target resource-poor countries.
10. Investments are urgently needed at national level – potentially reaching 1 billion dollars over the next three years. An additional 35 million dollars is needed immediately to support high priority actions by technical agencies at the global level over the next six months.

### **Recommended actions**

1. Support the development of integrated national plans for avian influenza control and human pandemic influenza preparedness and response.
2. Assist countries in aggressive control of avian influenza in birds, and deepen the understanding of the role of wild birds in virus transmission.
3. Nominate "rapid response" teams of experts to support epidemiological field investigations.
4. Strengthen country and regional capacity in surveillance, laboratory diagnosis, and alert and response systems.
5. Expand the network of influenza laboratories, with regional collaborative systems for access to reference laboratories.
6. Establish and integrate multi-country networks for the control or prevention of animal trans-boundary diseases, and regional support units as established in the Global Framework for the Progressive Control of Trans-boundary Animal Diseases.
7. Expand the global antiviral stockpile, and prepare standard operating practices for its rapid deployment to achieve early containment.
8. Assess the needs and strengthen veterinary infrastructure in line with OIE standards.
9. Map out a global strategy and work plan for coordinating antiviral and influenza vaccine research and development, and for increasing production capacity and equitable access.
10. Put forward proposals to the WHO Executive Board at its 117th (January 2006) meeting for immediate voluntary compliance with relevant articles of the International Health Regulations 2005.
11. Finalize detailed costing of country plans and the regional and global requirements to support them, in preparation for the January 2006 pledging meeting to be hosted by the Government of China.
12. Finalize a coordination framework building on existing mechanisms at the country level, and at the global level, building on international best practices.

## **Annex 2: WHO strategic action plan**

Concerning human health matters, four main opportunities to act were identified during the 7-9 November 2005 meeting: reduce high-risk behaviors associated with human infections; improve the detection, investigation, and reporting of human cases and, in so doing, strengthen the early warning system; contain an emerging pandemic virus; and increase pandemic preparedness. A fifth item – considered by many participants to be the most pressing need for adequate preparedness – concerned world capacity to manufacture sufficient quantities of pandemic vaccines and antiviral drugs, at sufficient speed, and to make these interventions broadly accessible to all countries.

These five actions formed the basis of the five-pronged strategic plan developed by WHO immediately after the meeting. The plan aims to achieve two over-arching objectives:

1. to ensure full exploitation of all opportunities to prevent the H5N1 virus from developing the ability to ignite a pandemic and, should this effort fail,
2. to ensure that measures are in place to mitigate the high levels of morbidity and mortality and social and economic disruption that can be expected during the next pandemic.

Each strategic action has a goal that contributes to these larger objectives.

Strategic action	Goal
1 <b>Reduce human exposure to the H5N1 virus</b>	Reduce opportunities for human infection and, in so doing, reduce opportunities for a pandemic virus to emerge
2 <b>Strengthen the early warning system</b>	Ensure that affected countries, WHO, and the international community have all data and clinical specimens needed for an accurate risk assessment
3 <b>Intensify rapid containment operations</b>	Prevent the H5N1 virus from further increasing its transmissibility among humans or delay its international spread
4 <b>Build capacity to cope with a pandemic</b>	Ensure that all countries have formulated and tested pandemic response plans and that WHO is fully able to perform its leadership role during a pandemic
5 <b>Coordinate global scientific research and development</b>	Ensure that pandemic vaccines and antiviral drugs are rapidly and widely available shortly after the start of a pandemic and that scientific understanding of the virus evolves quickly

The plan sets out expected results over the next two years and gives indicators for measuring progress. It also identifies seven institutional capacities that will be strengthened by the proposed strategic actions. Apart from preparing the world to cope with the present emergency situation, the strengthening of these capacities will improve the world's ability collectively to defend itself against many other emerging and epidemic-prone diseases.